P 030

DEPARTMENT OF TRADE AND INDUSTRY
DEPARTEMENT VAN HANDEL EN NYWERHEID

REPUBLIC OF SOUTH AFRICA REPUBLIEK VAN SUID-AFRIKA

LETTERS PATENT
(PATENTS ACT, 1978)

PATENTBRIEF
(WET OP PATENTE, 1978)

No. 95/0511

WHEREAS KOREN LABORATORIES PTY LTD
NADEMAAL
(Hereinafter called "the Patentee")
(Hieronder "die Patenthouer" genoem)

has applied to me for the grant of a patent in respect of an invention described and claimed in the complete specification
aansoek by my gedoen het om die verlening van 'n patent ten opsigte van 'n uitvinding wat beskryf is en waarop aanspraak

deposited at the Patent Office under the above-mentioned number, a copy of which is annexed, together with the relevant
gemaak word in die volledige spesifikasie wat by die Patentkantoor onder bovermelde nommer ingedien is en waarvan 'n

Form P.2;
afskrif aangeheg is tesame met die betrokke Vorm P. 2;

NOW THEREFORE these Letters Patent are to grant to the Patentee a patent, the effect of which shall be to grant to the
SO IS DIT dat hierdie Patentbrief aan die Patenthouer 'n patent verleen wat die uitwerking het dat, behoudens die

Patentee in the Republic, subject to the provisions of the Act, for the duration of the patent, the right to exclude other persons
bepalings van die Wet, aan die Patenthouer vir die duur van die patent in die Republiek die reg verleen word om ander

from making, using, exercising or disposing of the invention, so that he shall have and enjoy the whole profit and advantage
persone uit te sluit van die vervaardiging, aanwending, uitoefening of van die handsetting van die uitvinding, sodat hy al die

accruing by reason of the invention.
wins en voordeel wat uit die uitvinding voortspruit, verkry en geniet.

IN TESTIMONY WHEREOF the seal of the Patent Office has been affixed at Pretoria with effect from the
TER BETUIGING WAARVAN die seël van die Patentkantoor hierop te Pretoria aangebring is met ingang van die

29th day of MAY nineteen hundred and NINETY SIX
dag van eenduisend negehonderd

Registrar of Patents - Registrateur van Patente

See overleaf
Blaai om

G.P.-S. 019-0127

REPUBLIC OF SOUTH AFRICA

REGISTER OF PATENTS

OFFICIAL APPLICATION NO.	LODGING DATE: PROVISIONAL	ACCEPTANCE DATE
21 61 950511	22	47 11-3-96
INTERNATIONAL CLASSIFICATION	**LODGING DATE: COMPLETE**	**GRANTED DATE**
51 A61k	23 23rd January, 1995	1996-05-29

FULL NAME(S) OF APPLICANT(S)/PATENTEE(S)

71 KOREN LABORATORIES PTY LTD . A legal body organised and existing under the laws of Australia.

APPLICANTS SUBSTITUTED:	DATE REGISTERED
71	

ASSIGNEE(S)	DATE REGISTERED
71	

FULL NAME(S) OF INVENTOR(S)

72 David LUBOWSKI.

PRIORITY CLAIMED	COUNTRY	NUMBER	DATE
N.B. Use International abbreviation for country (See Schedule 4)	33 AU AU	31 PM 4247 PM 6395	32 4th March, 1994 22nd June, 1994

TITLE OF INVENTION

54 TREATMENT OF ANORECTAL DISORDERS.

ADDRESS OF APPLICANT(S)/PATENTEE(S)

10 Cecil Street, Paddington, New South Wales 2011, Australia.

ADDRESS FOR SERVICE	J & K REF:
74 JOHN & KERNICK, VAN DER STEL BLDG., PRETORIUS STR., PRETORIA	AP 31075 ZA

PATENT OF ADDITION NO.	DATE OF ANY CHANGE
61	

FRESH APPLICATION BASED ON	DATE OF ANY CHANGE

John & Kernick
FORM P1

REPUBLIC OF SOUTH AFRICA
PATENTS ACT, 1978
APPLICATION FOR A PATENT AND
ACKNOWLEDGEMENT OF RECEIPT
Section 30(1) - Regulation 39

REPUBLIC OF SOUTH AFRICA
REVENUE
23.1.95 R 200.00
REPUBLIEK VAN SUID AFRIKA
370

The grant of a Patent is hereby requested by the undermentioned applicant(s) on the present application filed in duplicate

21	01	Official application No.	22	Lodging date	J&K Reference
		95/0511		23rd January, 1995	AP 31075 ZA/PJW

71 Full Name(s) of applicants:
KOREN LABORATORIES PTY LTD . A legal body organised and existing under the laws of Australia.

Address(es) of applicant(s)
10 Cecil Street, Paddington, New South Wales 2011, Australia.

54 Title of Invention: TREATMENT OF ANORECTAL DISORDERS.

XX The applicant claims priority as set out in the accompanying form P2. The earliest priority claimed is - AU PM 4247 4th March, 1994.

This application is for a Patent of Addition to Patent/Application No. | 24 | 01 |

This application is a fresh application in terms of S 37 and based on application no. | 21 | 01 |

This application is accompanied by:

- 1a A single copy of a provisional specification of pages
- 1b Two copies of a complete specification of pages
- 2a Informal drawings of sheets
- 2b Formal drawings of sheets
- 3. Publication particulars and abstract (form P8 in duplicate)
- 4. A copy of Figure of the drawings for the abstract
- 5. Assignment of invention (from the inventors) or other evidence of title
- 6. Certified priority documents (documents)
- 7. Translation of priority documents (documents)
- 8. Assignment of priority rights
- 9. A copy of the form P2 and the specification of S.A Patent Application | 21 | 01 |
- 10. A declaration and power of attorney on form P3
- 11. Request for ante-dating on form P4
- 12. Request for classification on form P9
- 13a Request for delay of acceptance on form P4
- 13b

74 Address for Service: JOHN & KERNICK, PRETORIA.

Date 23rd January, 1995

Signature of Applicant

The duplicate will be returned to the applicant for service as proof of lodging but is not valid unless endorsed with official stamp.

Official date stamp
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1995 -01- 23
Registrar of patents
REGISTRATEUR VAN PATENTE, MODELLE, HANDELSMERKE EN OUTEURSREG

John & Kernick
FORM P7

REPUBLIC OF SOUTH AFRICA
PATENTS ACT, 1978

COMPLETE SPECIFICATION

(Section 30(1) - Regulation 28)

21 01 Official application No.	22 Lodging date	J&K Reference
95/0511	23rd January, 1995	AP 31075 ZA/PJW

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A61K	

71 Full Name(s) of Applicant(s)

KOREN LABORATORIES PTY LTD . A legal body organised and existing under the laws of Australia.

72 Full name(s) of Inventor(s)

David LUBOWSKI.

54. Title of invention

TREATMENT OF ANORECTAL DISORDERS.

TREATMENT OF ANORECTAL DISORDERS

The present invention relates to a new method of treating anorectal disorders in animals, and particularly in humans, by administering to a patient requiring such treatment specific compounds, as described hereafter. The invention is particularly concerned with the treatment of haemorrhoids and anal fissure in humans.

The treatment can be used with various anorectal disorders, including haemorrhoids, both internal and external, anal fissure, and generalised anal pain.

Various anal conditions such as haemorrhoids and fissure-in-ano, are associated with spasm of the internal anal sphincter. Up to the present time, no effective treatment is known for these conditions, other than various local surgical procedures. These surgical procedures involve stretching or cutting the anal sphincter in order to relieve the spasm. Also, topical ointments and creams are available, but these are not believed to have any direct influence on the anal conditions, but simply have analgesic or anti-inflammatory activity, in order to temporarily relieve the symptoms and pain. Sometimes these conditions occur when there is no measurable spasm. To date, no agent is known which can effectively relax the spasm of the anal sphincter muscle, or relax the muscle, and surgical treatment has been the only effective method of treatment of these conditions before the present time.

More specifically, haemorrhoids (also known as piles) are a varicose condition of the haemorrhoidal veins, causing painful swellings at the anus, as well as bleeding in some cases. With external haemorrhoids, the dilated veins form tumours on the outer side of the external sphincter, or are covered by the skin of the anal canal. Internal haemorrhoids occur when the swollen veins are beneath the mucous membrane within the sphincter. By the age of fifty, as many as 50% of people have haemorrhoids. The reason why haemorrhoids occur is not fully understood at present but may be caused by increased

intra-abdominal pressure which may be caused by pregnancy, or straining in passing stools, or alternatively it is believed that some hormonal influence may affect the rich network of blood vessels at the anus in such a way as to cause haemorrhoids to form.

The usual symptoms of haemorrhoids are bleeding, protrusion and pain. Ulcerated or thrombosed haemorrhoids are very painful. The pain caused by haemorrhoids can be severe or even incapacitating and methods of treatment of haemorrhoids have changed hardly at all in recent times. For severe pain, local anaesthetic can be applied topically and protruding internal haemorrhoids can be treated by rubber-band ligation. The usual therapy for haemorrhoids that cause only slight bleeding or minimal discomfort is warm sitz baths and stool softeners. Internal haemorrhoids that bleed persistently are treated by injection or by rubber-band ligation. Sometimes ointments and suppositories which are advertised widely for therapy of haemorrhoids can be used, but these, while of some assistance in relieving pain and discomfort, have no real therapeutic effect in curing the condition.

Anal fissure (fissure-in-ano) is a condition involving an acute longitudinal tear, or a chronic ovoid ulcer, in the stratified squamous epithelium of the anal canal. The exact causes of this condition is not known, though traumatic laceration from a hard or large stool may be involved. Fissures cause pain and bleeding with defecation. The pain typically occurs with or shortly following defecation, lasts for several hours, and then subsides until the next bowel movement.

It has been known for some time that the internal anal sphincter relaxes in response to rectal distension, which is known as "the rectanal inhibitory reflex". However little is known of the chemical mechanisms involved in this reflex. The nerves mediating the rectanal inhibitory reflex lie within the walls of the gut and are known as "enteric (intrinsic) inhibitory neurones". These neurones descend from the rectum to the internal anal sphincter and are known not to use classical neurotransmitter substances, such as

acetylcholine or noradrenaline. These nerves are classified as non-adrenergic, non-cholinergic (NANC) nerves. Recently, a variety of substances such as nitric oxide (NO), and carbon monoxide (CO) are thought to act as neurotransmitters in the gastrointestinal tract, and have been reported as being involved in the nerve mediated relaxation of the internal anal sphincter. In the body, nitric oxide is synthesised from L-arginine in a reaction catalysed by NO synthase. The NO synthase enzyme exhibits a high degree of substrate specificity, (for example NO is not produced from D-arginine), and is dependent on several cofactors including the presence of Ca^{2+} ions, calmodulin and reduced nicotinamide adenine dinucleotide phosphate. NO is very soluble, and diffuses rapidly in the body. It has a very short half life of only three seconds, and is inactivated by the formation of nitrate (NO_3^-) after contact with the superoxide anion (O_2^-). CO is produced from heme by the enzyme heme oxygenase.

Until the present invention, it had not been realised that substances which mediate either directly or indirectly relaxation of the anal sphincter may be used in the treatment of haemorrhoids, anal fissure, and other anorectal disorders.

The invention in one form therefore concerns a method of treating various anorectal conditions in an animal (including a human) which comprises administering to a subject in need of such treatment an effective amount of at least one substance which mediates relaxation of the anal sphincter. Preferably the substance modulates or influences NO or CO neurotransmitter ability. By this is meant that the substance has one or more of the effects of increasing the levels of NO or CO in the anorectal region, increasing the half life of endogenous NO or CO, increasing the affinity of NO or CO for their receptor in the anal sphincter, blocking inhibitors of NO or CO binding to their respective receptors, and increasing access of NO or CO to their receptor. It is to be understood that this invention is not limited to substances which modulate or influence NO or CO neurotransmitter ability. Rather, the invention extends to the use of any substance or

combination of substances which mediate relaxation of the anal sphincter, which may hereinafter be referred to as anal sphincter relaxation substances.

Levels of NO or CO in the anorectal region may be increased by substances which are a source of NO or CO themselves (ie breakdown to form NO or CO in the presence of enzymes and/or other compounds in the body, or form NO or CO as a result of activating compounds which form part of the composition) or which stimulate endogenous compounds (such as L-arginine or heme oxygenase) within the body to produce NO or CO for subsequent relaxation of the anal sphincter. Any substance which modulates or influences neurotransmitter ability in the manner described above may be utilised in this invention. Preferred substances which may be used according to the invention include nitrates, vasodilators, amino acids which break down to form NO, calcium channel blockers and the like.

Any nitrate compound or compound which breaks down in the body to form NO and which is non-toxic may be utilized according to this invention compounds which may be utilized include compounds which fall within the classes known as mononitrate, dinitrates, trinitrates, tetranitrates and the like. For example, nitrate compounds may be selected from isosorbide dinitrate, amyl nitrate, pentaerythritol tetranitrate, nitroglycerine (glyceryl nitrate) and the like. Nitroglycerine is particularly preferred for use in treating anorectal disorders such as haemorrhoids, anal fissure and similar conditions.

Vasodilator compounds, particularly those that influence NO neurotransmitter ability, can also be utilized in the invention, and these include hydralazine, and sodium or other salts of nitroprusside (nitroprusside being known as a donor of NO). Any vasodilator compound which is pharmaceutically acceptable and which relaxes the anal sphincter may be used in the invention. Examples of such compounds include alpreolol, amlodipine, atenolol, diltiazem, felodipine, limaprost, metaprolol, nicardipine, nifedipine, oxprenolol, prinadol, propranolol and the like.

Still other anal sphincter relaxation substances which may be used in the invention include acetyl choline, prostaglandins, vasoactive intestinal polypeptide, histamine, L-arginine, and the like. Compounds which stimulate heme oxygenase production within the body may also be utilized in the invention.

Mixtures of more than one of the aforementioned active ingredients can also be utilized in the invention. For example, nitroglycerine can be utilized together with a long-acting nitrate, to allow longer lasting relief from haemorrhoid and other anorectal pain.

As mentioned previously, many anorectal conditions can be treated in accordance with the invention, including internal and external haemorrhoids, anal fissure, anal pain, and other, similar, conditions.

The active ingredients of the invention may be administered orally, topically, transdermally, parenterally such as by direct injection into the site of anorectal pain, by inhalation, transdermally, intrarectally, or to tissue surrounding the anus. Preferably, the active ingredients of the invention are administered directly to the anus. Non-oral administration routes are preferred for nitrate compounds such as nitroglycerine which may be inactivated by the liver. For topical administration, formulations such as ointments, creams, lotions and solutions are preferred. Long acting slow release dermal or other such device patches which release nitroglycerine or other active ingredients may be utilised. Rectal suppositories containing active ingredients as described are also contemplated by the invention.

The amount of active ingredient to be applied will vary, in accordance with the method of application chosen the activity of the active ingredient. For example, an active ingredient may be present in a composition in an amount from about 0.0001% w/w to 5% w/w or more. When nitroglycerine is the active ingredient, therapeutic compositions may contain the nitroglycerine in an amount of approximately 0.001 to 0.2% w/w, together

with an hormone carriers component or other components. More preferably the amount of nitroglycerine present in a therapeutic composition is between about 0.1% and 0.2% w/w.

Composition or formulations for the administration of active agents according to the invention may be prepared with any suitable excipient or diluent as are well known in the art, such as are described in Remingtons Pharmaceutical Sciences (*10th Edition, Mack Publishing Company, Philadelphia, USA)* which is incorporated herein by reference. Particularly preferred are those carriers and excipients well known in the art for anorectal administration, such as for the treatment of haemorrhoids, fissure and the like.

The formulations of the present invention may also include other ingredients which act as analgesics or anti-inflammatory agents. For example, in addition to the active ingredients, as described above, further analgesic and/or anti-inflammatory agents include benzocaine, lignocaine, xylocaine, cinchocaine, hydrocortisone, prednisolone, prednisone, adrenalin or methylhydroxybenzoate, are just some examples. Calcium channel blockers may also be further active ingredients. Preferred secondary ingredients include compounds which have previously been used to treat haemorrhoids, anal fissure, and other anal conditions. The amounts of the secondary ingredients present are chosen according to standard practice in the art.

This invention also relates to a method for the manufacture of a medicament for the treatment of anorectal conditions in an animal, which comprises admixing at least one substance which mediates relaxation of the anal sphincter with one or more pharmaceutically acceptable excipients or diluents.

The invention further relates to the use of one or more anal sphincter relaxation substance in the manufacture of a medicament for the treatment of anorectal conditions in animals.

In still another aspect, the invention relates to the use of one or more anal sphincter relaxation substances in the treatment of anorectal conditions in animals.

The invention is now described with reference to various examples. Whilst these examples relate to the use of nitroglycerine it is to be understood that the invention is not, of course, restricted to the use of this compound.

EXAMPLE 1

Ointment Formulation

A formulation was prepared containing glyceryl trinitrate (GTN - nitroglycerine) in an amount of 0.2% w/w, with the remainder of the formulation being soft yellow paraffin BP. A second formulation was made in the same manner, but with the glycerol trinitrate being present in an amount of 0.1% w/w, with the same ointment base.

EXAMPLE 2

Treatment of Anal Fissure Condition

A number of patients presenting to the Colorectal Unit attached to a large Sydney Hospital were entered into a trial. All the patients had symptomatic anal fissure, which would otherwise have required surgery. Subjects having anal fissure were chosen for the trial since the effects of the treatment are able to be monitored very easily.

Forty three patients were entered into a double-blind, randomised placebo-controlled trial. Subjects were randomly allocated either a 0.2% GTN paste, as described in Example 1, or otherwise a placebo containing no active ingredients, but identical in all other respects. Each subject underwent a detailed anorectal physiology study to test pressures within the anal canal. Each subject also filled in a pain score on a linear

analogue scale, and progress in the healing of the fissure was monitored by two observers who were blinded to the form of treatment being given.

The twenty four patients who received GTN all experienced a successful chemical sphincterotomy resulting in a statistically significant improvement in pain, fissure grade and anal canal pressure compared with the placebo group of nineteen patients.

EXAMPLE 3

Treatment of Haemorrhoids

The 0.2% and 0.1% cream as described in Example 1 was tested with ten patients suffering from internal haemorrhoids. All patients exhibited haemorrhoid relief including reduction in haemorrhoid size, extent of bleeding, and less discomfort.

While the present invention is described with reference to various Examples, these Examples are not intended to be limiting on the invention, and other obvious modifications of the present invention can be utilized without departing from its broad scope as described previously.

The claims defining the invention are as follows:

1. The use of at least one substance which mediates the relaxation of the anal sphincter in a method for the treatment of anorectal conditions in animals which comprises administering to a subject in need of such treatment an effective amount of said substance.

2. The use of a substance according to claim 1 wherein said substance is a source of nitric oxide or carbon monoxide.

3. The use of a substance according to claim 1 wherein said substance is a nitrate compound.

4. The use of a substance according to claim 3 wherein said nitrate compound is selected from isosorbide dinitrate, amylnitrate, pentaerythritol, tetranitrate, and nitroglycerine.

5. The use of a substance according to claim 1 wherein said substance is nitroglycerine.

6. The use of a substance according to claim 1 wherein said substance is a vasodilator.

7. The use of a substance according to claim 6 wherein said vasodilator is selected from alpreolol, amlodipine, atenolol, diltiazem, felodipine, limaprost, metaprolol, nicardipine, nifedipine, oxprenolol, prinadol, and propranolol.

8. The use of a substance according to claim 1 wherein said substance is selected from acetyl choline, L-arginine, vasoactive intestinal polypeptide, histamine or a prostaglandin.

9. The use of a substance according to claim 1 wherein said substance is administered in association with an analgesic and/or anti-inflammatory agent.

10. The use of a substance according to any one of claims 1 to 9 wherein said substance is administered in association with one or more pharmaceutically acceptable carriers.

11. The use of a substance according to claim 1 wherein said substance is administered topically, subcutaneously, transdermally, parenterally, or interrectally.

12. The use of a substance according to claim 1 for the treatment of haemorrhoids.

13. The use of a substance according to claim 1 for the treatment of anal fissure.

14. The use of a substance for the treatment of anorectal conditions in an animal which comprises administering to a subject in need of such treatment an effective amount of at least one substance which modulates nitric oxide or carbon monoxide neurotransmitter ability.

15. The use of a substance according

17. The use of a substance according to claim 14 wherein said nitrate compound is selected from isosorbide dinitrate, amylnitrate, pentaerythritol tetranitrate, and nitroglycerine.

18. The use of a substance according to claim 14 wherein said substance is nitroglycerine.

19. The use of a substance according to claim 14 wherein said substance is a vasodilator.

20. The use of a substance according to claim 19 wherein said vasodilator is selected from alpreolol, amlodipine, atenolol, diltiazem, felodipine, limaprost, metaprolol, nicardipine, nifedipine, oxprenolol, prinadol and propranolol.

21. The use of a substance according to claim 14 wherein said substance is selected from acetyl choline and L-arginine.

22. The use of a substance according to claim 14 wherein said substance is administered in association with an analgesic and/or anti-inflammatory agent.

23. The use of a substance according to claim 14 wherein said substance is administered in association with one or more pharmaceutically acceptable carriers.

24. The use of a substance according to claim 14 wherein said substance is administered topically, subcutaneously, transdermally, parenterally, or interrectally.

25. The use of a substance according to claim 14 for the treatment of haemorrhoids.

26. The use of a substance according to claim 14 for the treatment of anal fissure.

27. A method for the manufacture of a medicament for the treatment of anorectal conditions in an animal, which comprises admixing at least one substance which mediates relaxation of the anal sphincter with one or more pharmaceutically acceptable excipients or diluents.

28. A method according to claim 27 wherein said substance which mediates relaxation of the anal sphincter is selected from a compound according to any one of claims 2 through 8.

29. Use of one or more anal sphincter relaxation substances in the treatment of anorectal conditions in animals.

30. Use of one or more anal sphincter relaxation substances in the manufacture of a medicament for the treatment of anorectal conditions in animals.

31. An agent for the treatment of anorectal conditions in animals which comprises at least one substance which mediates the relaxation of the anal sphincter.

32. An agent according to claim 31 wherein said substance which mediates the relaxation of the anal sphincter is a substance according to any one of claims 1 through 8.

DATED THIS THE 6TH DAY OF FEBRUARY 1995

JOHN & KERNICK
FOR THE APPLICANT